Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2108163

REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19

SUPPLEMENTARY APPENDIX

Table of Contents

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Supplementary Methods

Trial Oversight

Regeneron designed the trial; gathered the data, together with the trial investigators; and analyzed the data. Regeneron vouches for the fidelity of the trial to the protocol.

The investigators, site personnel, and Regeneron employees who were involved in collecting and analyzing data were unaware of the treatment-group assignments. An independent data monitoring committee monitored unblinded data to make recommendations about trial modification and termination.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

Symptoms Evolution of COVID-19 (SE-C19)

The Symptoms Evolution of COVID-19 (SE-C19) instrument was an electronic diary that was completed daily from Day 1 to Day 29. The SE-C19 was initially developed based on the CDC symptom list and available published literature specific to patients with COVID-19. It included a list of 23 symptoms feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhea, headache, red or

watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomachache, rash, sneezing, sputum or phlegm, runny nose). Patients indicated which of the 23 symptoms they experienced in the last 24 hours and then rated each symptom selected at its worst moment in that period on a scale of mild, moderate or severe.

In parallel to the main clinical trial, patient and clinician interviews were performed to confirm the content validity of the newly developed SE-C19 and psychometric validation was conducted using blinded phase 1/2 data to explore the reliability and validity of the measure and refine a symptom endpoint. The results indicated 19 of the original 23 items being most valid, reliable and relevant to outpatients with COVID-19 (i.e., sneezing, rash, vomiting and confusion were excluded) and refinement of the response options to three-categories (0 – none, 1 – mild/moderate, 2 – severe). The detailed, rigorous scientific methods implemented and results of these additional studies will be published independently.

Endpoints – Additional Description

Time to Covid-19 symptoms resolution

Time to Covid-19 symptoms resolution was defined as time from randomization to the first day during which the patient scored “no symptom’ (score=0) on all 19 symptoms except cough, fatigue, and headache, which could have been scored as “mild/moderate symptom” (score=1) or “no symptom” (score=0).

Missing Data Handling

Missing data for virology endpoints was handled as follows: Analysis-positive polymerase chain reaction (PCR) results below the lower limit of quantification (LLOQ) of 714 copies/ml (2.85 $\log_{10}$ copies/ml) were imputed as half the LLOQ (357 copies/ml) and negative PCR results were imputed as 0 $\log_{10}$ copies/ml (1 copy/ml).

Patients with missing baseline symptom assessment were not included in the analysis of the symptom resolution endpoint. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 were censored at day 29.

Measurement of REGN10933 and REGN10987 in Serum

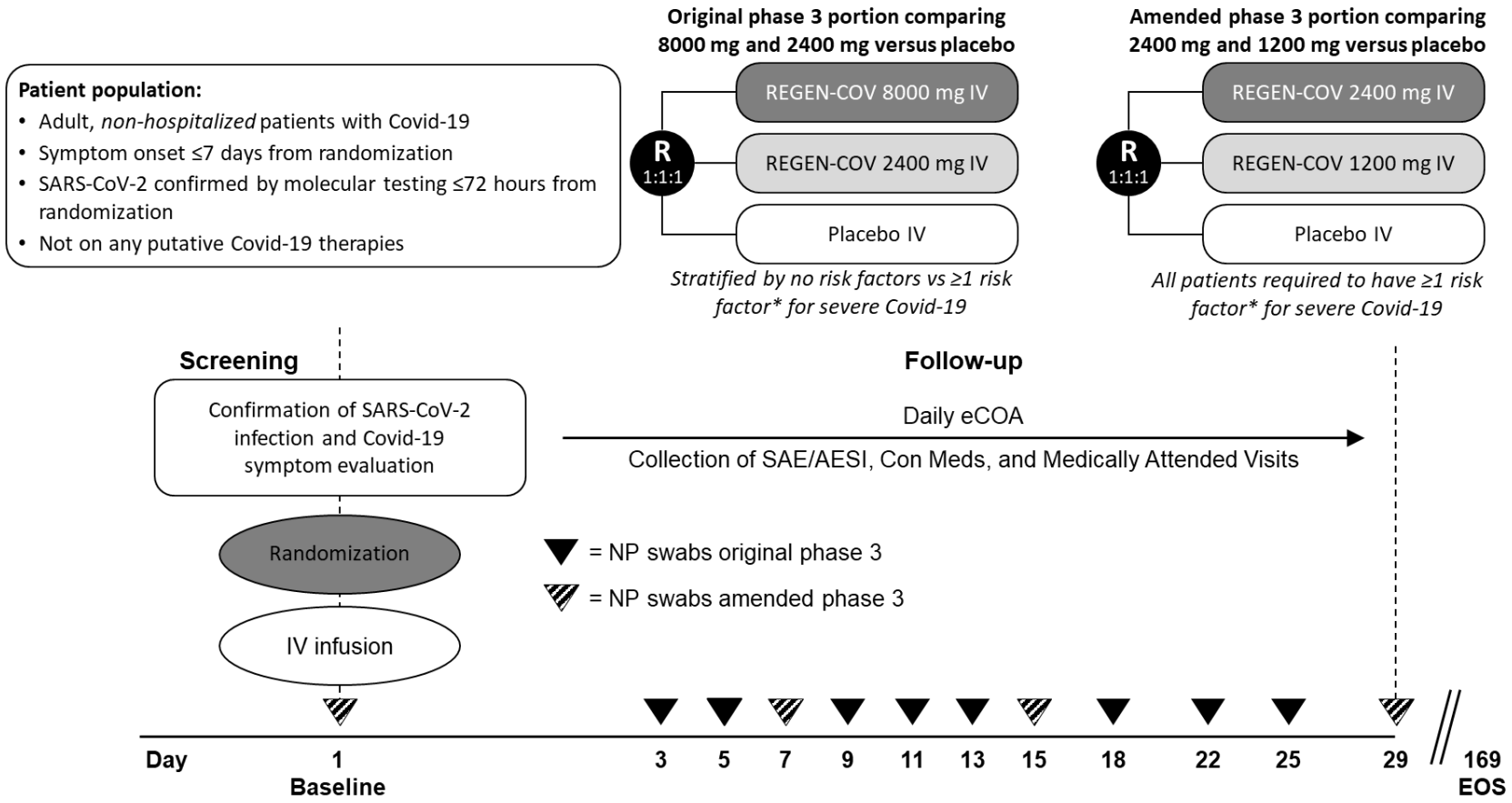
Prior to protocol amendment 6, serum for drug concentration analysis was collected from all patients randomized to 2400 mg IV, 8000 mg IV, or placebo at pre-dose (at the screening or baseline visit), day 1 at the end of the infusion, and day 29. After protocol amendment 6, serum for drug concentration analysis was collected from patients randomized to 1200 mg IV, 2400 mg IV, or placebo in a PK sub-study at pre-dose (at the screening or baseline visit), day 29, and day 120.

The human serum concentrations of REGN10933 (casirivimab) and REGN10987 (imdevimab) were measured using validated immunoassays which employ streptavidin microplates from Meso Scale Discovery (MSD, Gaithersburg, MD, USA). The methods

utilized two anti-idiotypic monoclonal antibodies, each specific for either REGN10933 or REGN10987, as the capture antibodies. Captured REGN10933 and REGN10987 were detected using two different, non-competing anti-idiotypic monoclonal antibodies, each also specific for either REGN10933 or REGN10987. The bioanalytical methods specifically quantitated the levels of each anti-SARS-CoV-2 spike monoclonal antibody separately, with no interference from the other antibody. The assay has an LLOQ of 0.156 µg/ml for each analyte in the undiluted serum sample.

Supplementary Figures

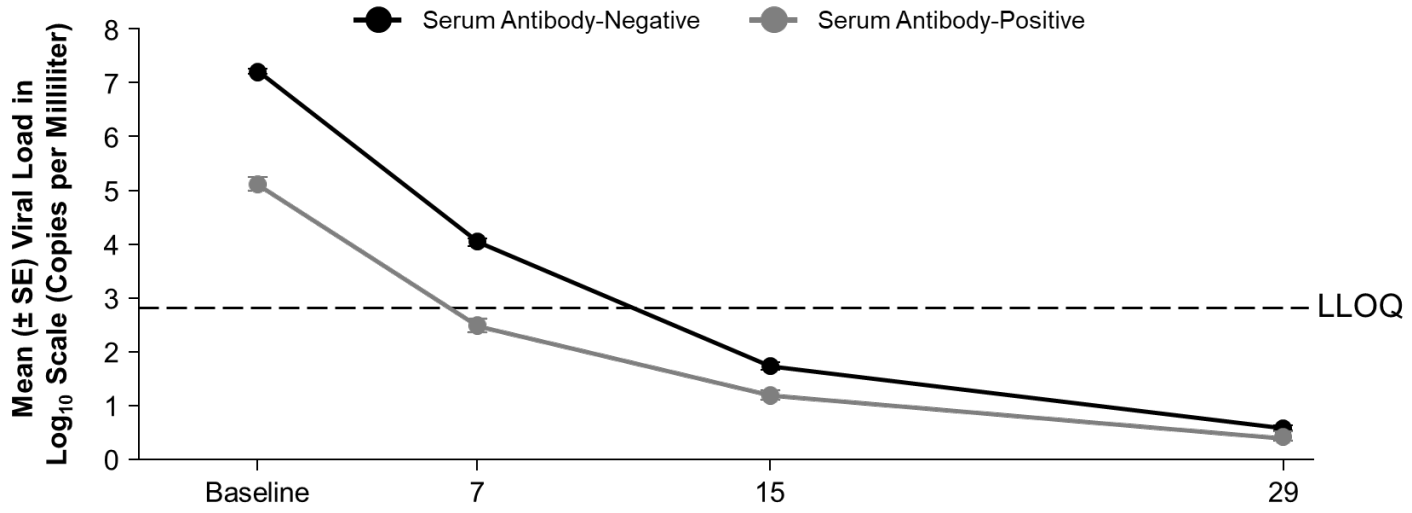
Figure S1. Schematic Overview of the Study Design



AESI, adverse event of special interest; con med, concomitant medication; eCOA, electronic clinical outcome assessment; EOS, end of study; IV, intravenous(ly); NP, nasopharyngeal; R, randomized; SAE, serious adverse event.

* Risk factors were defined as age ≥50 years, obesity (BMI >30 kg/m^2), cardiovascular disease, including hypertension, type 1 or 2 diabetes mellitus, chronic lung disease, including asthma, chronic liver disease, chronic kidney disease, and immunocompromised.

Figure S2. Viral Load Over Time in the Placebo Arm by Baseline Serum Antibody Status

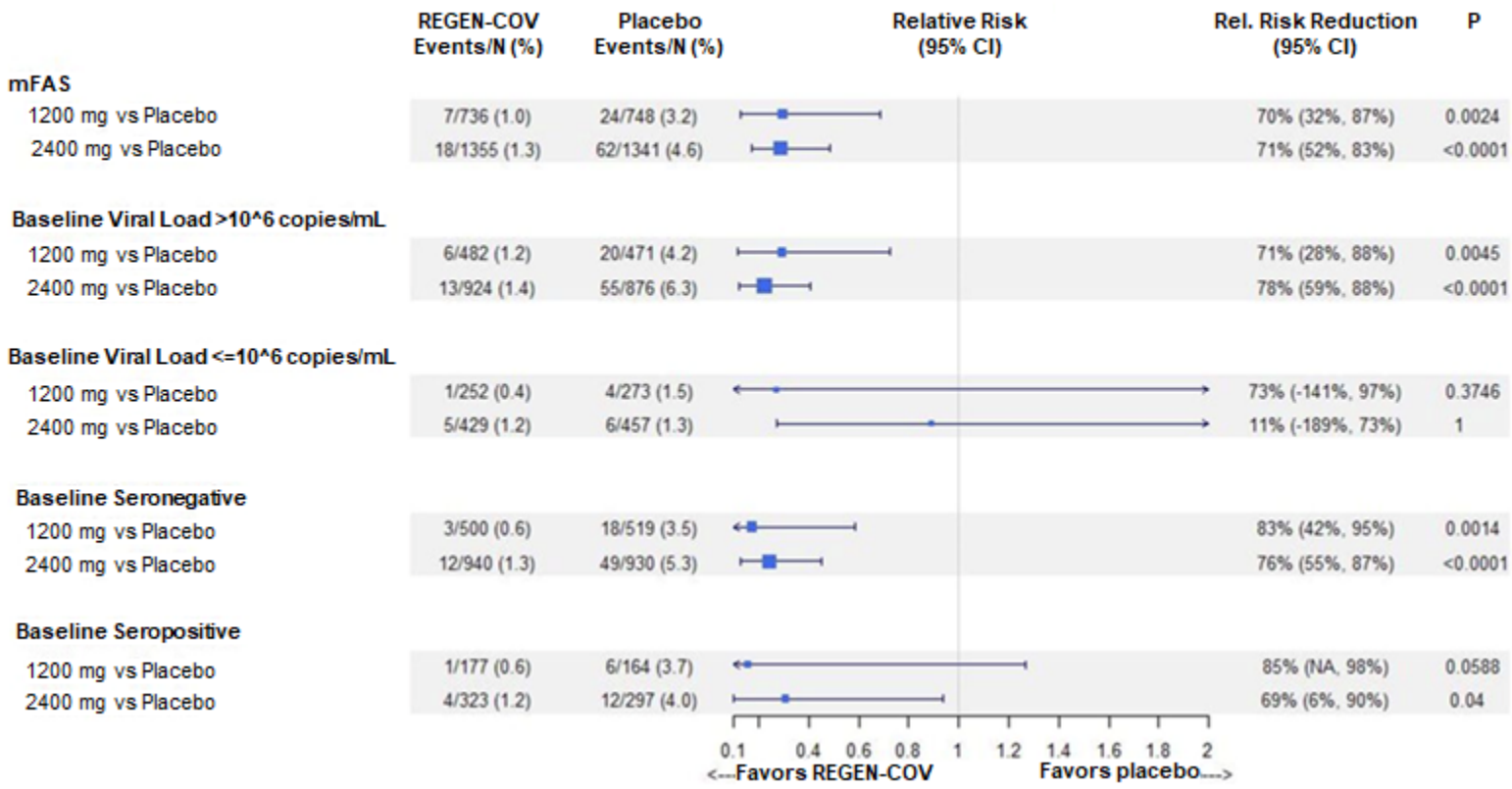


Number of patients:				
Serum Antibody-Negative	926	857	836	846
Serum Antibody-Positive	295	275	265	261

LLOQ, lower limit of quantification; SE, standard error.

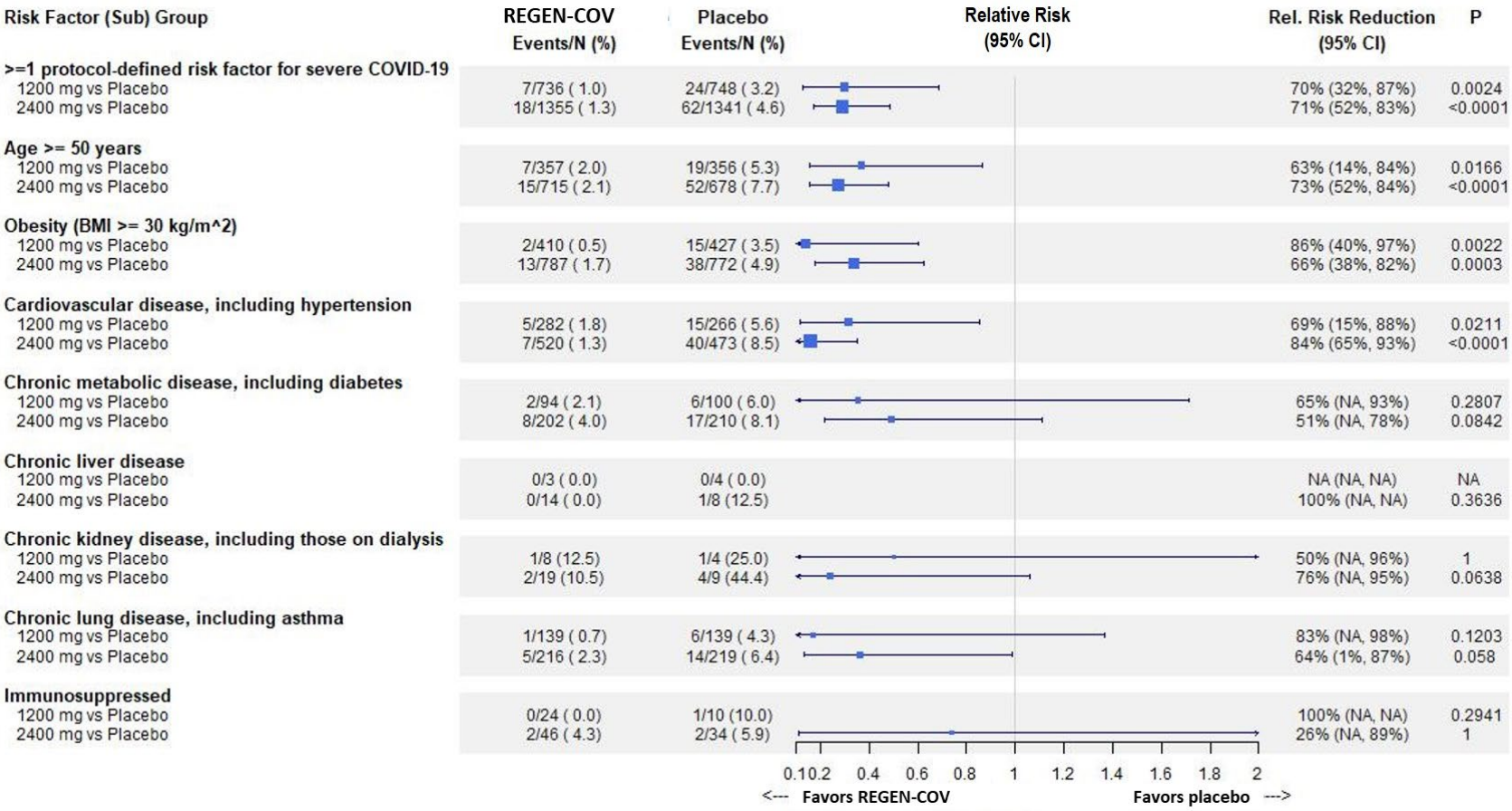
Figure S3. Forest Plots: COVID-19-related Hospitalization or All-Cause Death Through Day 29

A. Subgroups: Baseline viral load and serum antibody status



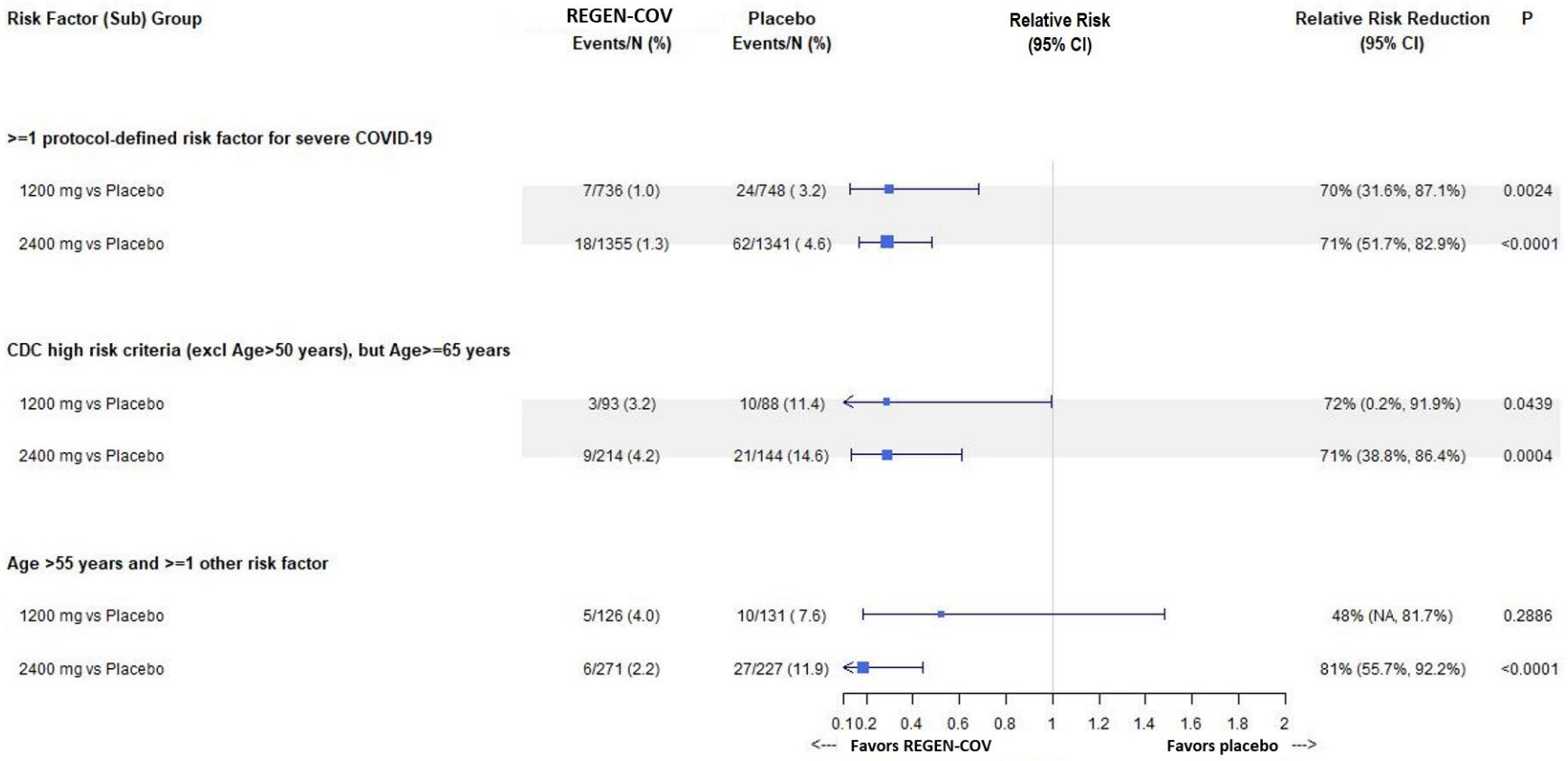
CI, confidence interval; mFAS, modified full analysis set.

B. Subgroups: Protocol-defined risk factors



BMI, body mass index; CI, confidence interval.

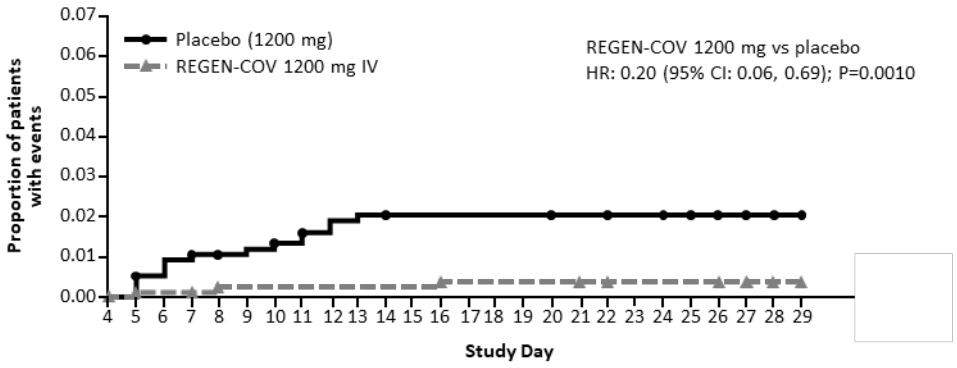
C. Subgroups: Other risk factor combinations



CDC, Centers for Disease Control and Prevention; CI, confidence interval.

Figure S4. COVID-19-related Hospitalization or All-Cause Death – Day 4 through Day 29

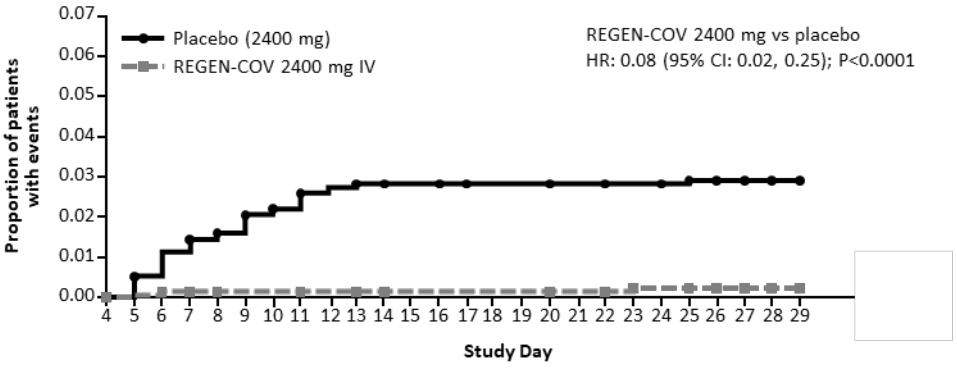
A. COVID-19–related hospitalization or all-cause death – Day 4 through Day 29 – REGEN-COV 1200 mg IV single dose



Placebo vs 1200 mg	739	733	728	726	720	717	716	716	716	715	702	699	669	598
REGEN-COV 1200 mg IV	732	726	725	723	723	723	723	721	721	720	708	708	695	624

CI, confidence interval; HR, hazard ratio; IV, intravenous.

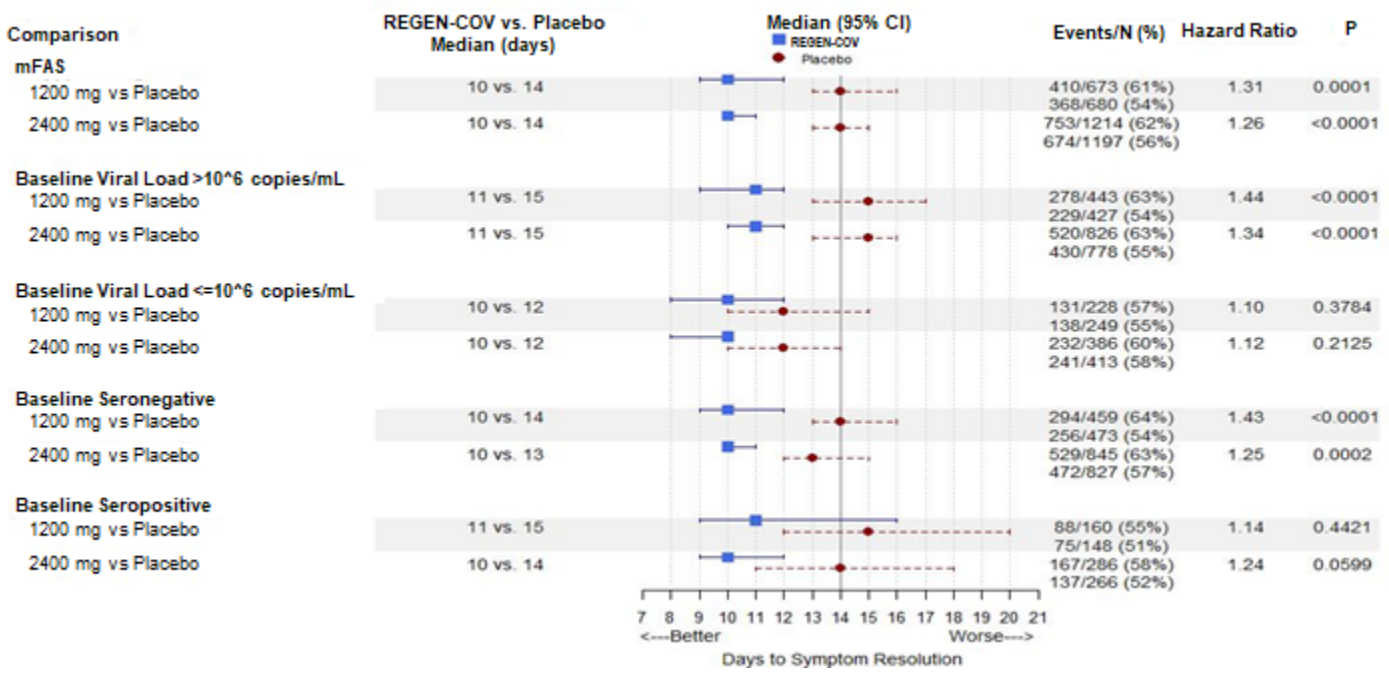
B. COVID-19–related hospitalization or all-cause death – Day 4 through Day 29 – REGEN-COV 2400 mg IV single dose



Placebo vs 2400 mg	1316	1306	1291	1279	1267	1263	1260	1258	1258	1257	1242	1238	1170	1052
REGEN-COV 2400 mg IV	1336	1334	1330	1329	1327	1326	1324	1324	1324	1323	1314	1312	1247	1113

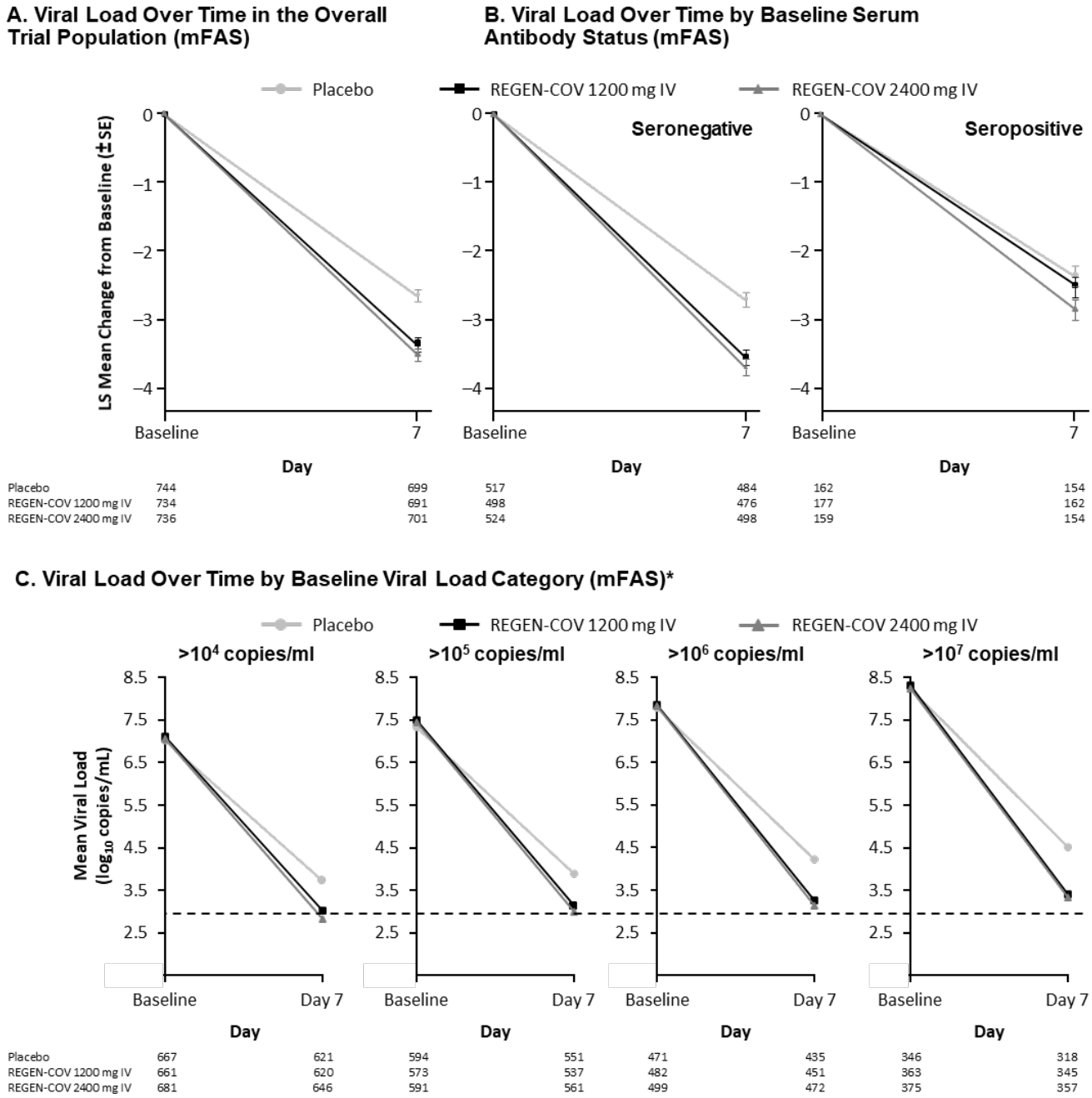
CI, confidence interval; HR, hazard ratio; IV, intravenous.

Figure S5. Forest Plot: Time to Symptoms Resolution



CI, confidence interval; mFAS, modified full analysis set.

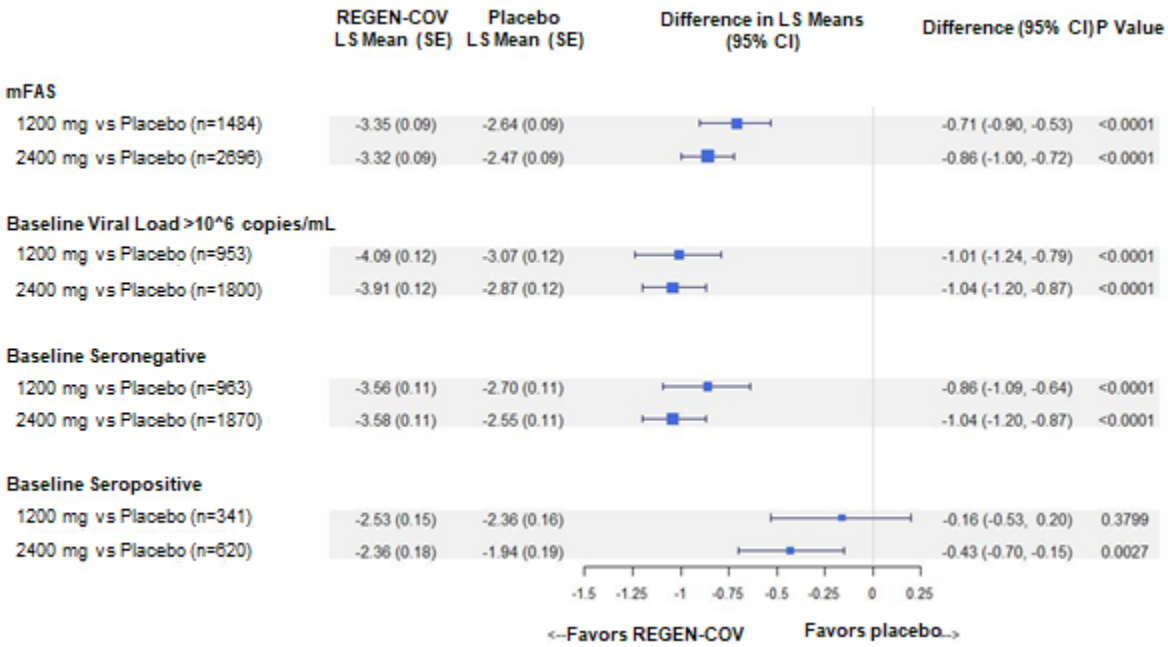
Figure S6. Virologic Efficacy – Amended Phase 3 Portion



IV, intravenous(ly); mFAS, modified full analysis set; SE, standard error.

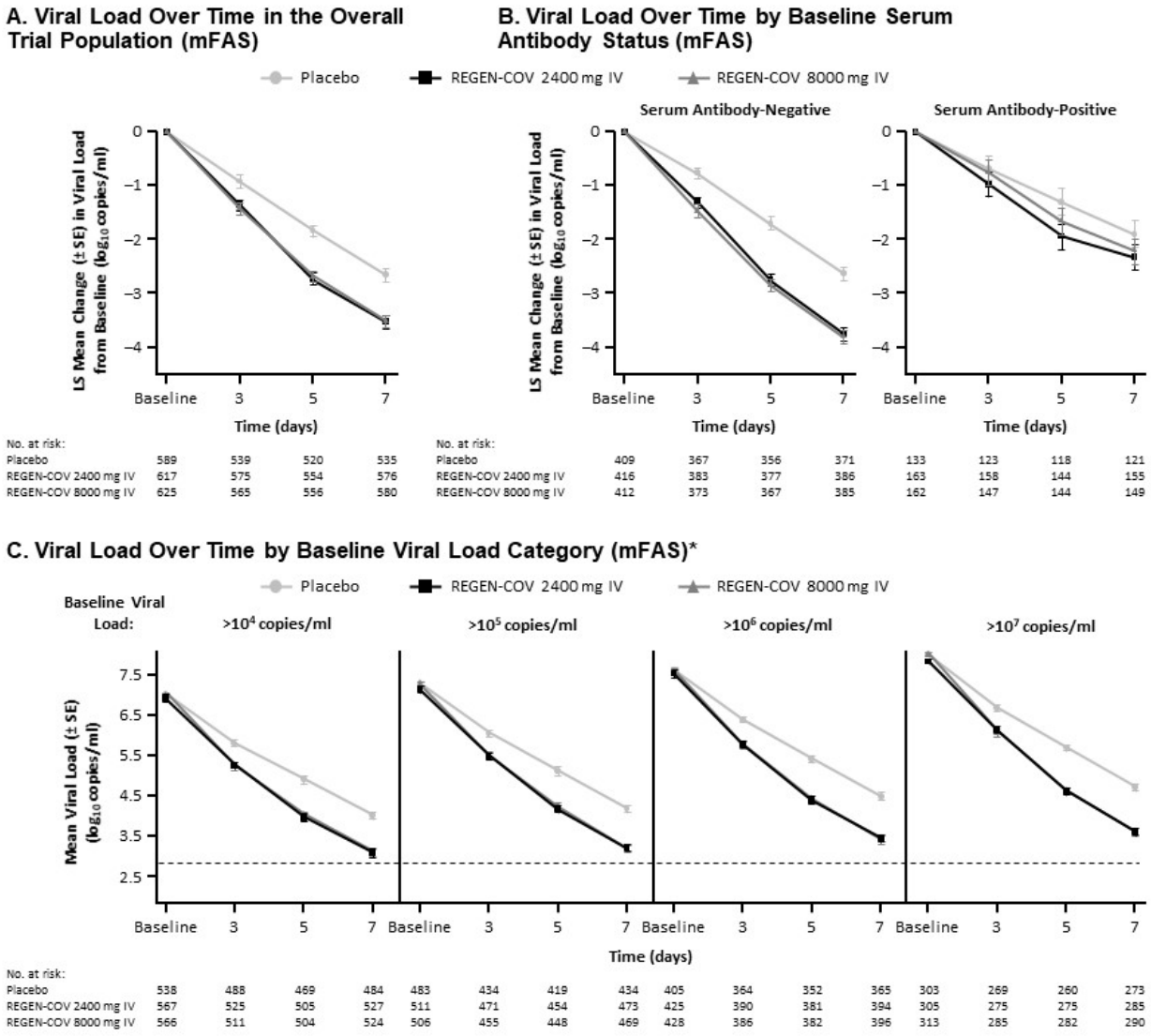
* The lower limit of detection (dashed line) is 714 copies per milliliter (2.85 $\log_{10}$ copies per milliliter).

Figure S7. Forest Plot: Virologic Efficacy – Amended Phase 3 Portion



CI, confidence interval; LS, least squares; mFAS, modified full analysis set; SE, standard error.

Figure S8. Virologic Efficacy – Original Phase 3 Portion



mFAS, modified full analysis set; IV, intravenous; SE, standard error.

* The lower limit of detection (dashed line) is 714 copies per milliliter (2.85 $\log_{10}$ copies per milliliter).

Supplementary Tables

Table S1. Phase 3 Primary Analysis Hierarchical Testing Order

The analysis of the primary endpoint (proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29) and key secondary endpoint (time to symptom resolution) will be conducted at the overall α=0.05. The endpoints will be tested hierarchically in the following order, adjusting for interim analysis:

Hierarchy Number	Description
1	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGEN-COV 2400 mg group versus placebo
2	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGEN-COV 1200 mg group versus placebo
3	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGEN-COV 2400 mg group versus placebo
4	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGEN-COV 2400 mg group versus placebo
5	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGEN-COV 1200 mg group versus placebo
6	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGEN-COV 1200 mg group versus placebo
7	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGEN-COV 2400 mg group versus placebo
8	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGEN-COV 1200 mg group versus placebo
9	Time to COVID-19 symptoms resolution in the mFAS for REGEN-COV 2400 mg group versus placebo
10	Time to COVID-19 symptoms resolution in the mFAS for REGEN-COV 1200 mg group versus placebo

mFAS, modified full analysis set.

Table S2: Demographic and Baseline Medical Characteristics (mFAS)

Characteristic*	REGEN-COV 2400 mg (n=1355)	Placebo (2400 mg) (concurrent) (n=1341)	REGEN-COV 1200 mg (n=736)	Placebo (1200 mg) (concurrent) (n=748)	Total (n=4057)
Demographics					
Median age (IQR) — year	50.0 (39.0–60.0)	50.0 (37.0–58.0)	48.5 (37.0–57.5)	48.0 (35.0–57.0)	50.0 (38.0–59.0)
Baseline age category — no. (%)					
Age ≥50 years	715 (52.8)	678 (50.6)	357 (48.5)	356 (47.6)	2101 (51.8)
Age ≥65 years	214 (15.8)	144 (10.7)	93 (12.6)	88 (11.8)	548 (13.5)
Male sex — no. (%)	656 (48.4)	633 (47.2)	364 (49.5)	352 (47.1)	1977 (48.7)
Hispanic or Latino ethnic group — no. (%)†	464 (34.2)	471 (35.1)	312 (42.4)	295 (39.4)	1424 (35.1)
Race — no. (%)†					
White	1161 (85.7)	1136 (84.7)	595 (80.8)	611 (81.7)	3426 (84.4)
Black or African American	67 (4.9)	66 (4.9)	38 (5.2)	38 (5.1)	204 (5.0)
Asian	52 (3.8)	56 (4.2)	38 (5.2)	36 (4.8)	172 (4.2)
American Indian or Alaska Native	19 (1.4)	13 (1.0)	17 (2.3)	10 (1.3)	52 (1.3)
Unknown	28 (2.1)	43 (3.2)	36 (4.9)	37 (4.9)	122 (3.0)

Not reported	24 (1.8)	26 (1.9)	10 (1.4)	15 (2.0)	74 (1.8)
Median weight (IQR) — kg	87.50 (75.15–102.10)	87.90 (74.30–103.00)	86.20 (74.40–102.10)	86.20 (72.80–102.40)	87.80 (74.80–103.00)
Body-mass index‡	31.09±6.33	31.19±6.63	31.54±7.31	31.07±6.46	31.33±6.76
Obesity — no. (%)§	787 (58.1)	772 (57.6)	410 (55.7)	427 (57.1)	2353 (58.0)
At least one risk factor for severe Covid-19 — no. (%)¶	1355 (100)	1341 (100)	736 (100)	748 (100)	4057 (100)
Medical/Clinical Characteristics					
Positive baseline qualitative RT-PCR — no. (%)	1353 (99.9)	1333 (99.4)	734 (99.7)	744 (99.5)	4045 (99.7)
Baseline viral load in nasopharyngeal swab (raw values)					
No. of patients	1353	1333	734	744	4045
Mean viral load — (10^6) copies/ml	250.74± 764.3	293.65± 1061.1	439.04± 1703.6	372.54± 1300.5	286.58± 1070.8
Median viral load (range) — (10^6) copies/ml	10.30 (0–10600)	9.01 (0–16100)	8.37 (0–29700)	7.12 (0–16100)	9.55 (0–29700)
Baseline viral load in nasopharyngeal swab (log_{10} scale)					
No. of patients	1353	1333	734	744	4045
Mean viral load — log_{10} copies/ml	6.72±1.71	6.66±1.75	6.73±1.86	6.63±1.82	6.69±1.75

Median viral load (range) — log_{10} copies/ml	7.01 (2.6–10.0)	6.95 (2.6–10.2)	6.92 (2.6–10.5)	6.85 (2.6–10.2)	6.98 (2.6–10.5)
Baseline serum C-reactive protein level					
No. of patients	1242	1243	713	724	3742
Mean level — mg/l	11.99±23.24	12.97±24.54	13.24±23.77	13.1±24.97	12.87±24.52
Median level (range) — mg/l	4.615 (0.11–354.16)	4.940 (0.10–242.73)	4.910 (0.11–238.53)	4.865 (0.16–227.45)	4.850 (0.10–354.16)
Baseline serum antibody status — no. (%)					
Negative	940 (69.4)	930 (69.4)	500 (67.9)	519 (69.4)	2782 (68.6)
Positive	323 (23.8)	297 (22.1)	177 (24.0)	164 (21.9)	959 (23.6)
Other	92 (6.8)	114 (8.5)	59 (8.0)	65 (8.7)	316 (7.8)
Median time from symptom onset to randomization (IQR) — days	3.0 (2–5)	3.0 (2–5)	3.0 (2–5)	3.0 (2–4)	3.0 (2–5)

IQR, interquartile range; RT-PCR, reverse-transcriptase polymerase chain reaction; SD, standard deviation.

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Placebo (2400 mg) concurrent group (n=1341) also includes those patients receiving placebo concurrent with the 1200 mg REGEN-COV group (n=748). Total number of patients includes 8000 mg group (625 patients).
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Obesity is defined as a body-mass index of greater than or equal to 30.
¶ Risk factors for hospitalization include an age of more than 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised (immunosuppression or receipt of immunosuppressants).

Table S3. Protocol-Defined Risk Factors for Severe Covid-19 (mFAS)

Protocol-defined risk factor — no. (%)	**Placebo (n=1341)**	**REGEN-COV 1200 mg (n=736)**	**REGEN-COV 2400 mg (n=1355)**	**REGEN-COV 8000 mg (n=625)**	**Total (n=4057)**
Age ≥50 years	678 (50.6)	357 (48.5)	715 (52.8)	351 (56.2)	2101 (51.8)
Obesity (BMI ≥30 kg/m^2)	772 (57.6)	410 (55.7)	787 (58.1)	384 (61.4)	2353 (58.0)
Cardiovascular disease, including hypertension	473 (35.3)	282 (38.3)	520 (38.4)	196 (31.4)	1471 (36.3)
Chronic lung disease, including asthma	219 (16.3)	139 (18.9)	216 (15.9)	92 (14.7)	666 (16.4)
Type 1 or 2 diabetes mellitus	210 (15.7)	94 (12.8)	202 (14.9)	97 (15.5)	603 (14.9)
Chronic kidney disease, including those on dialysis	9 (0.7)	8 (1.1)	19 (1.4)	9 (1.4)	45 (1.1)
Chronic liver disease	8 (0.6)	3 (0.4)	14 (1.0)	11 (1.8)	36 (0.9)
Immunocompromised*	34 (2.5)	24 (3.3)	46 (3.4)	16 (2.6)	120 (3.0)

BMI, body mass index; mFAS, modified full analysis set.

* The most common immunosuppressive conditions were rheumatoid arthritis, HIV/AIDS, and systemic lupus erythematosus; the most common immunosuppressive medications were hydroxychloroquine, antimetabolites, and TNF inhibitors.

Table S4. Demographic and Baseline Medical Characteristics (mFAS) – 8000 mg REGEN-COV

Characteristic*	REGEN-COV 8000 mg (n=625)	Placebo (8000 mg) (concurrent) (n=593)
Demographics		
Median age (IQR) — year	51.0 (40.0–59.0)	50.0 (39.0–58.0)
Baseline age category — no. (%)		
Age ≥50 years	351 (56.2)	322 (54.3)
Age ≥65 years	97 (15.5)	56 (9.4)
Male sex — no. (%)	324 (51.8)	281 (47.4)
Hispanic or Latino ethnic group — no. (%)†	177 (28.3)	176 (29.7)
Race — no. (%)†		
White	534 (85.4)	525 (88.5)
Black or African American	33 (5.3)	28 (4.7)
Asian	26 (4.2)	20 (3.4)
American Indian or Alaska Native	3 (0.5)	3 (0.5)
Unknown	15 (2.4)	6 (1.0)
Not reported	14 (2.2)	11 (1.9)
Median weight (IQR) — kg	89.85 (76.20–106.60)	88.50 (75.00–104.00)

Body-mass index‡	31.90±7.23	31.35±6.85
Obesity — no. (%)§	384 (61.4)	345 (58.2)
At least one risk factor for severe Covid-19 — no. (%)¶	625 (100)	593 (100)
Medical/Clinical Characteristics		
Positive baseline qualitative RT-PCR — no. (%)	625 (100)	589 (99.3)
Baseline viral load in nasopharyngeal swab (raw values)		
No. of patients	625	589
Mean viral load — (10^6) copies/ml	170.03 ± 555.7	194.01 ± 628.9
Median viral load (range) — (10^6) copies/ml	10.10 (0–6090)	11.20 (0–6780)
Baseline viral load in nasopharyngeal swab (log_{10} scale)		
No. of patients	625	589
Mean viral load — log_{10} copies/ml	6.64 ± 1.67	6.70 ± 1.66
Median viral load (range) — log_{10} copies/ml	7.00 (2.6–9.8)	7.05 (2.6–9.8)
Baseline serum C-reactive protein level		
No. of patients	544	519
Mean level — mg/l	14.21 ± 28.03	12.79 ± 23.94
Median level (range) — mg/l	5.07 (0.18–228.07)	5.02 (0.10–242.73)

Baseline serum antibody status — no. (%)		
Negative	412 (65.9)	411 (69.3)
Positive	162 (25.9)	133 (22.4)
Other	51 (8.2)	49 (8.3)
Median time from symptom onset to randomization (IQR) — days	3.0 (2–5)	3.0 (2–5)

IQR, interquartile range; RT-PCR, reverse-transcriptase polymerase chain reaction; SD, standard deviation.

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Obesity is defined as a body-mass index of greater than or equal to 30.
¶ Risk factors for hospitalization include an age of more than 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised (immunosuppression or receipt of immunosuppressants).

Table S5. Proportion of Patients in the Placebo Arms with ≥1 Covid-19-related Hospitalization or All-cause Death by Baseline Viral Load Category and Baseline Serum Antibody Status

End Point	Placebo (concurrent with REGEN-COV 2400 mg)	Placebo (concurrent with REGEN-COV 1200 mg)
Proportion of patients with ≥1 Covid-19-related hospitalization or all-cause death		
Baseline viral load category: high viral load (>10^6 copies/mL)		
No. of patients	876	471
Patients with event within 29 days — no. (%)	55 (6.3)	20 (4.2)
Baseline viral load category: low viral load (≤10^6 copies/mL)		
No. of patients	457	273
Patients with event within 29 days — no. (%)	6 (1.3)	4 (1.5)
Proportion of patients with ≥1 Covid-19-related hospitalization or all-cause death		
Baseline serum antibody status: negative		
No. of patients	930	519
Patients with event within 29 days — no. (%)	49 (5.3)	18 (3.5)
Baseline serum antibody status: positive		
No. of patients	297	164
Patients with event within 29 days — no. (%)	12 (4.0)	6 (3.7)
Baseline serum antibody status: other		
No. of patients	114	65
Patients with event within 29 days — no. (%)	1 (0.9)	0

Table S6. Viral Load in the Placebo Arm by With and Without Hospitalization or Death and by Baseline Serum Antibody Status

Baseline Serum Antibody Status:	Covid-19-related Hospitalization or Death	Baseline SARS-CoV-2 Viral Load (log_{10} copies/ml) (Mean ± SD)	Day 7 SARS-CoV-2 Viral Load (log_{10} copies/ml) (Mean ± SD)
All			
n=1272	No	6.62 ± 1.77	3.60 ± 2.13
n=61	Yes	7.54 ± 1.18	5.36 ± 1.35
Negative			
n=877	No	7.16 ± 1.49	4.03 ± 2.01
n=48	Yes	7.61 ± 1.09	5.41 ± 1.36
Positive			
n=283	No	5.04 ± 1.62	2.46 ± 2.04
n=12	Yes	7.06 ± 1.35	5.08 ± 1.39

SD, standard deviation.

Table S7. Proportion of Patients with ≥1 Covid-19-related Hospitalization or All-cause Death

End Point	REGEN-COV 2400 mg (n=1355)	Placebo (2400 mg) (concurrent) (n=1341)	REGEN-COV 1200 mg (n=736)	Placebo (1200 mg) (concurrent) (n=748)
Proportion of patients with ≥1 Covid-19-related hospitalization or all-cause death*				
Patients with event within 29 days — no. (%)	18 (1.3)	62 (4.6)	7 (1.0)	24 (3.2)
Relative risk reduction vs placebo — percentage points	71.3		70.4	
95% CI†	51.7, 82.9		31.6, 87.1	
Proportion of patients with hospitalization				
Patients with event within 29 days — no. (%)	17 (1.3)	59 (4.4)	6 (0.8)	23 (3.1)
Relative risk reduction vs placebo — percentage points	71.5		73.5	
95% CI†	51.3, 83.3		35.3, 89.1	
Proportion of patients with all-cause death				
Patients with event within 29 days — no. (%)	1 (<0.1)	3 (0.2)	1 (0.1)	1 (0.1)
Relative risk reduction vs placebo — percentage points	67.0		-1.6	
95% CI†	-216.7, 96.6		-1522, 93.6	

CI, confidence interval.

* Primary endpoint.
† 95% CI used the Farrington-Manning method.

Table S8. Proportion of Patients with ≥1 All-Cause Hospitalization or Death

End Point	REGEN-COV 2400 mg (n=1355)	Placebo (2400 mg) (concurrent) (n=1341)	REGEN-COV 1200 mg (n=736)	Placebo (1200 mg) (concurrent) (n=748)
Proportion of patients with ≥1 all-cause hospitalization* or all-cause death*				
Patients with event within 29 days — no. (%)	20 (1.5)	66 (4.9)	7 (1.0)	26 (3.5)
Relative risk reduction vs placebo — percentage points	70.0		72.6	
95% CI†	50.8, 81.7		37.4, 88.0	

CI, confidence interval.

* Related or not to Covid-19

† 95% CI used the Farrington-Manning method.

Table S9. Proportion of Patients with ≥1 Covid-19-related MAV or All-cause Death

End Point*	REGEN-COV 2400 mg (n=1355)	Placebo (2400 mg) (concurrent) (n=1341)	REGEN-COV 1200 mg (n=736)	Placebo (1200 mg) (concurrent) (n=748)
Proportion of patients with ≥1 Covid-19-related MAV or all-cause death				
Patients with event within 29 days — no. (%)	43 (3.2)	109 (8.1)	20 (2.7%)	51 (6.8)
Relative risk reduction vs placebo — percentage points	61.0		60.1	
95% CI†	44.9, 72.3		33.8, 76.0	
Proportion of patients with hospitalization				
Patients with event within 29 days — no. (%)	17 (1.3)	59 (4.4)	6 (0.8)	23 (3.1)
Relative risk reduction vs placebo — percentage points	71.5		73.5	
95% CI†	51.3, 83.3		35.3, 89.1	
Proportion of patients with emergency room visit				
Patients with event within 29 days — no. (%)	9 (0.7)	16 (1.2)	2 (0.3)	10 (1.3)
Relative risk reduction vs placebo — percentage points	44.3		79.7	
95% CI†	-25.5, 75.3		7.5, 95.5	
Proportion of patients with urgent care visit				
Patients with event within 29 days — no. (%)	3 (0.2)	7 (0.5)	1 (0.1)	5 (0.7)
Relative risk reduction vs placebo — percentage points	57.6		79.7	
95% CI†	-63.7, 89.0		-73.6, 97.6	
Proportion of patients with physician office/telemedicine visit				

Patients with event within 29 days — no. (%)	13 (1.0)	24 (1.8)	10 (1.4)	12 (1.6)
Relative risk reduction vs placebo — percentage points	46.4		15.3	
95% CI[†]	-4.8, 72.6		-94.8, 63.2	
Proportion of patients with all-cause death				
Patients with event within 29 days — no. (%)	1 (<0.1)	3 (0.2)	1 (0.1)	1 (0.1)
Relative risk reduction vs placebo — percentage points	67.0		-1.6	
95% CI[†]	-216.7, 96.6		-1522, 93.6	

CI, confidence interval; MAV, medically-attended visit.

* A patient with multiple types of events was only counted to the worst level event, following this decreasing order: all-cause death, hospitalization, ER, urgent care, physician office visit/telemedicine.
[†] 95% CI used the Farrington-Manning method.

Table S10. Hospitalization Outcomes: Length of Stay, Admission to an ICU, and Mechanical Ventilation

End Point	REGEN-COV 2400 mg (n=1355)	Placebo (2400 mg) (concurrent) (n=1341)	REGEN-COV 1200 mg (n=736)	Placebo (1200 mg) (concurrent) (n=748)
Days of hospitalization due to COVID-19 per patient				
No. of patients	18	62	7	24
Mean (SD)	8.6 ± 7.07	10.0 ± 7.16	7.0 ± 8.04	8.4 ± 6.74
Median (IQR)	6.0 (3.0–11.0)	7.0 (5.0–13.0)	4.0 (3.0–6.0)	5.5 (4.0–10.5)
Proportion of patients admitted to an ICU				
Patients with event within 29 days — no. (%)	6 (0.4)	18 (1.3)	3 (0.4)	7 (0.9)
Relative risk reduction vs placebo — percentage points	67.0		56.4	
95% CI*	17.2, 86.9		-67.8, 88.7	
Proportion of patients requiring mechanical ventilation				
Patients with event within 29 days — no. (%)	1 (<0.1)	6 (0.4)	1 (0.1)	2 (0.3)
Relative risk reduction vs placebo — percentage points	83.5		49.2	
95% CI*	-36.8, 98.0		-459.2, 95.4	

CI, confidence interval; ICU, intensive care unit, IQR, interquartile range, SD, standard deviation.

* 95% CI used the Farrington-Manning method.

Table S11. Proportion of Patients with ≥1 Covid-19-related Hospitalization, Emergency Room Visits, or All-cause Death

End Point	REGEN-COV 2400 mg (n=1355)	Placebo (2400 mg) (concurrent) (n=1341)	REGEN-COV 1200 mg (n=736)	Placebo (1200 mg) (concurrent) (n=748)
Proportion of patients with events				
Patients with event within 29 days — no. (%)	27 (2.0)	78 (5.8)	9 (1.2)	34 (4.5)
Relative risk reduction vs placebo — percentage points	65.7		73.1	
95% CI*	47.3, 77.7		44.3, 87.0	

CI, confidence interval.

* 95% CI used the Farrington-Manning method.

Table S12. Proportion of Patients with ≥1 Covid-19-related Hospitalization or All-cause Death – 8000 mg REGEN-COV

End Point	REGEN-COV 8000 mg (n=625)	Placebo (8000 mg) (concurrent) (n=593)
Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death*		
Patients with event within 29 days — no. (%)	13 (2.1)	38 (6.4)
Relative risk reduction vs placebo — percentage points	67.5	
95% CI†	39.7, 82.5	
Proportion of patients with hospitalization		
Patients with event within 29 days — no. (%)	13 (2.1)	36 (6.1)
Relative risk reduction vs placebo — percentage points	65.7	
95% CI†	36.0, 81.6	
Proportion of patients with all-cause death		
Patients with event within 29 days — no. (%)	0	2 (0.3)
Relative risk reduction vs placebo — percentage points	100.0	
95% CI†	n/a	

CI, confidence interval.

* Primary endpoint.
† 95% CI used the Farrington-Manning method.

Table S13. Proportion of Patients with ≥1 Covid-19-related MAV or All-cause Death – 8000 mg REGEN-COV

End Point*	REGEN-COV 8000 mg (n=625)	Placebo (8000 mg) (concurrent) (n=593)
Proportion of patients with ≥1 Covid-19-related MAV or all-cause death		
Patients with event within 29 days — no. (%)	26 (4.2)	58 (9.8)
Relative risk reduction vs placebo — percentage points	57.5	
95% CI†	33.4, 72.8	
Proportion of patients with hospitalization		
Patients with event within 29 days — no. (%)	13 (2.1)	36 (6.1)
Relative risk reduction vs placebo — percentage points	65.7	
95% CI†	36.0, 81.6	
Proportion of patients with emergency room visit		
Patients with event within 29 days — no. (%)	3 (0.5)	6 (1.0)
Relative risk reduction vs placebo — percentage points	52.6	
95% CI†	-88.8, 88.1	
Proportion of patients with urgent care visit		
Patients with event within 29 days — no. (%)	2 (0.3)	2 (0.3)
Relative risk reduction vs placebo — percentage points	5.1	
95% CI†	-571.4, 86.6	

Proportion of patients with physician office/telemedicine visit		
Patients with event within 29 days — no. (%)	8 (1.3)	12 (2.0)
Relative risk reduction vs placebo — percentage points	36.7	
95% CI†	-53.6, 74.0	
Proportion of patients with all-cause death		
Patients with event within 29 days — no. (%)	0	2 (0.3)
Relative risk reduction vs placebo — percentage points	100.0	
95% CI†	n/a	

CI, confidence interval; MAV, medically-attended visit.

* A patient with multiple types of events was only counted to the worst level event, following this decreasing order: all-cause death, hospitalization, ER, urgent care, physician office visit/telemedicine.
† 95% CI used the Farrington-Manning method.

Table S14. Clinical Efficacy in Low-Risk Patients – Original Phase 3 Portion

End Point†	Placebo (n=369)*	REGEN-COV 2400 mg (n=344)*	REGEN-COV 8000 mg (n=327)*
Proportion of patients with ≥1 Covid-19-related MAV or all-cause death†			
Patients with event within 29 days — no. (%)	5 (1.4)	3 (0.9)	2 (0.6)
Relative risk reduction vs placebo — percentage points		35.6	54.9
Proportion of patients with hospitalization†			
Patients with event within 29 days — no. (%)	2 (0.5)	0	0
Relative risk reduction vs placebo — percentage points		100	100
Proportion of patients with emergency room visit†			
Patients with event within 29 days — no. (%)	1 (0.3)	1 (0.3)	0
Relative risk reduction vs placebo — percentage points		-7.3	100
Proportion of patients with urgent care visit†			
Patients with event within 29 days — no. (%)	0	1 (0.3)	1 (0.3)
Relative risk reduction vs placebo — percentage points		n/a	n/a
Proportion of patients with physician office/telemedicine visit†			
Patients with event within 29 days — no. (%)	2 (0.5)	1 (0.3)	1 (0.3)
Relative risk reduction vs placebo — percentage points		46.4	43.6

Proportion of patients with all-cause death†			
Patients with event within 29 days — no. (%)	0	0	0
Relative risk reduction vs placebo — percentage points		n/a	n/a
Time to Covid-19 symptoms resolution			
Median	12.0	9.0	10.0
95% CI‡	10.0, 15.0	7.0, 10.0	8.0, 11.0
Hazard ratio vs. placebo§		1.42	1.33
95% CI§		1.16, 1.75	1.07, 1.64

CI, confidence interval; MAV, medically-attended visit.

* Patients without a risk factor for severe Covid-19; enrolled only in the original phase 3 portion of the trial.
† A patient with multiple types of events was only counted to the worst level event, following this decreasing order: all-cause death, hospitalization, ER, urgent care, physician office visit/telemedicine.
‡ Two-sided 95% CI is computed by Brookmeyer and Crowley method (log log transformation).
§ The hazard ratio and 95% confidence interval are estimated using Cox proportional hazard model with terms for treatment and country as fixed effects. Hazard ratio >1 implies REGEN-COV is better than placebo.

Table S15. Treatment-Emergent Adverse Events Leading to Death

System Organ Class Preferred Term	**Placebo (n=1476)**	**REGEN-COV 1200 mg IV (n=827)**	**REGEN-COV 2400 mg IV (n=1512)**	**REGEN-COV 8000 mg IV (n=689)**	**Total (n=4504)**
			no. of patients (percent)		
Number of patients with at least one treatment-emergent adverse event leading to death					
TEAE leading to death	5 (0.3)	1 (0.1)	1 (<0.1)	0	7 (0.2)
Treatment-emergent adverse event leading to death by system organ class and preferred term					
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	1 (<0.1)	0	1 (<0.1)	0	2 (<0.1)
Acute respiratory distress syndrome	1 (<0.1)	0	0	0	1 (<0.1)
Hypoxia	0	1 (0.1)	0	0	1 (<0.1)
Respiratory failure	1 (<0.1)	0	0	0	1 (<0.1)
Infections and infestations					
COVID-19	1 (<0.1)	0	0	0	1 (<0.1)
COVID-19 pneumonia	1 (<0.1)	0	0	0	1 (<0.1)
Pneumonia	1 (<0.1)	0	0	0	1 (<0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)					
Tumor obstruction	1 (<0.1)	0	0	0	1 (<0.1)

IV, intravenous(ly).

Table S16. Treatment-Emergent Serious Adverse Events and Adverse Events of Special Interest

System Organ Class Preferred Term*	**Placebo (n=1843)**	**REGEN-COV 1200 mg IV (n=827)**	**REGEN-COV 2400 mg IV (n=1849)**	**REGEN-COV 8000 mg IV (n=1012)**	**Total (n=5531)**
	no. of patients (percent)[†]				
Serious treatment-emergent adverse events by system organ class and preferred term					
Infections and infestations					
COVID-19	18 (1.0%)	1 (0.1%)	5 (0.3%)	5 (0.5%)	29 (0.5%)
COVID-19 pneumonia	14 (0.8%)	2 (0.2%)	4 (0.2%)	5 (0.5%)	25 (0.5%)
Pneumonia	17 (0.9%)	2 (0.2%)	3 (0.2%)	1 (<0.1%)	23 (0.4%)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	7 (0.4%)	0	1 (<0.1%)	1 (<0.1%)	9 (0.2%)
Hypoxia	6 (0.3%)	1 (0.1%)	1 (<0.1%)	1 (<0.1%)	9 (0.2%)
Acute respiratory failure	3 (0.2%)	0	2 (0.1%)	1 (<0.1%)	6 (0.1%)
Respiratory distress	2 (0.1%)	0	0	0	2 (<0.1%)
Metabolism and nutrition disorders					
Dehydration	2 (0.1%)	0	0	0	2 (<0.1%)
Hyponatraemia	2 (0.1%)	0	0	0	2 (<0.1%)
Adverse events of special interest by preferred term					
COVID-19	11 (0.6%)	2 (0.2%)	4 (0.2%)	2 (0.2%)	19 (0.3%)
Dyspnoea	9 (0.5%)	3 (0.4%)	3 (0.2%)	1 (<0.1%)	16 (0.3%)
Cough	2 (0.1%)	3 (0.4%)	2 (0.1%)	1 (<0.1%)	8 (0.1%)
Pneumonia	6 (0.3%)	2 (0.2%)	0	0	8 (0.1%)
COVID-19 pneumonia	4 (0.2%)	2 (0.2%)	0	1 (<0.1%)	7 (0.1%)
Headache	2 (0.1%)	2 (0.2%)	1 (<0.1%)	1 (<0.1%)	6 (0.1%)
Dizziness	1 (<0.1%)	2 (0.2%)	1 (<0.1%)	0	4 (<0.1%)
Nausea	0	2 (0.2%)	0	1 (<0.1%)	3 (<0.1%)
Pulmonary congestion	1 (<0.1%)	0	0	2 (0.2%)	3 (<0.1%)
Nasal congestion	2 (0.1%)	0	0	0	2 (<0.1%)

IV, intravenous(ly).

* Term included if ≥2 patients in any of the individual dose groups.

† A patient who reported 2 or more adverse events with different preferred terms within the same system organ class is counted only once in that system organ class. A patient who reported 2 or more adverse events with the same preferred term is counted only once for that term. A patient who reported 2 or more adverse events with the same preferred term is counted only once for that term. If a patient had more than one occurrence in the same event category, only the most related was counted.

Table S17. Mean (SD) [N] Pharmacokinetic Parameters of REGN10933 and REGN10987 in Serum

PK Parameter	REGN10933 (casirivimab)*			REGN10987 (imdevimab)*		
	600 mg	1200 mg	4000 mg	600 mg	1200 mg	4000 mg
C_{eoi} (mg/L)†	185 (74.5) [158]	321 (106) [553]	1049 (317) [388]	192 (78.9) [171]	321 (112) [580]	1049 (308) [400]
C_{28} (mg/L)‡	46.4 (22.5) [127]	73.2 (27.2) [609]	238 (86.1) [482]	38.3 (19.6) [127]	60.0 (22.9) [610]	192 (70.2) [469]
Estimated $t_{1/2}$ in days (90% CI)§	28.8 (16.5, 41.1)			25.5 (17.4, 33.7)		

C, concentration; eoi, end of infusion; IV, intravenous; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life.

* Mean (SD) [N], where N is number of observations
† Concentration at the end of infusion (1 hour)
‡ Observed concentration 28 days after dosing, i.e., on day 29
§ Based on 2-compartment population pharmacokinetic models developed for casirivimab and imdevimab from approximately 3700 patients across different REGEN-COV clinical trials, including this study (2067). Half-life estimates represent values for the 1200 mg IV, 2400 mg IV, and 8000 mg IV doses combined.